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PERSPECTIVES

Is a monovalent vaccine against enterovirus 71 sufficient? A review of enterovirus 71 vaccine development based on enterovirus surveillance in Taiwan

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Non-polio enteroviruses are among the most common viral infectious agents. More than 60 serotypes of enteroviruses are classified into four groups: coxsackievirus A (CA), coxsackievirus B (CB), echovirus (Echo), poliovirus and new enterovirus. While most enteroviral cases are either asymptomatic or have mild symptoms (e.g., mild upper respiratory problems), some cases exhibit symptoms such as hand-foot-mouth disease (HFMD), herpangina, aseptic encephalitis, viral meningitis and acute hemorrhagic conjunctivitis. Severe complications have potentially lethal consequences.[1]

EV71 was first isolated in California in 1969. In the 1970s, two EV71 outbreaks caused a number of deaths in Bulgaria and Hungary, but the enterovirus threat did not receive much attention until epidemics erupted in Malaysia and Taiwan in 1997 and 1998, respectively. Since then, HFMD surveillance systems have been established successively in Malaysia, Singapore, Thailand, China and Vietnam. According to regional surveillance data, EV71 and CA16 are the major pathogenic virus types for HFMD in the Southeast Asian countries.[2,3]

Various surveillance systems were established in Taiwan after the 1998 EV71 outbreak. First, the contracted virological laboratory system is responsible for enterovirus isolation and the typing of clinical samples collected by sentinel physicians. Second, physicians should report enterovirus infections with severe complications as class C diseases to the National Notifiable Surveillance System. Third, the Real-time Outbreak and Disease Surveillance System (RODS) replaced the physician-based Sentinel Surveillance System for HFMD and herpangina in 2007. The new system monitors enterovirus consultation trends in hospital emergency rooms to provide timely surveillance data. Fourth, syndromic surveillance through the National Health Insurance Claims Database (NHICD) covering 99% of outpatient, inpatient and emergency room visits in Taiwan was established in April 2009. It collects the number of visits for enterovirus infection to estimate disease burden.

Community virus surveillance statistics from Taiwan's virological contract laboratories indicate that CA is the most prevalent serotype. Of these, CA16 is the most common, and high isolation rates were seen in 2000–2003, 2005[4,5], 2007 and 2010. EV71 activity was high in 2000, 2001, 2005[4,5] and 2008. However, because 19–78% of virus strains could not be identified by commercial immunofluorescent kits in 2002–2006, Taiwan's Centers for Disease Control (TCDC) has developed several immunofluorescent kits for detecting CA2, 4, 5, 6, 10 and 21 since 2005. These

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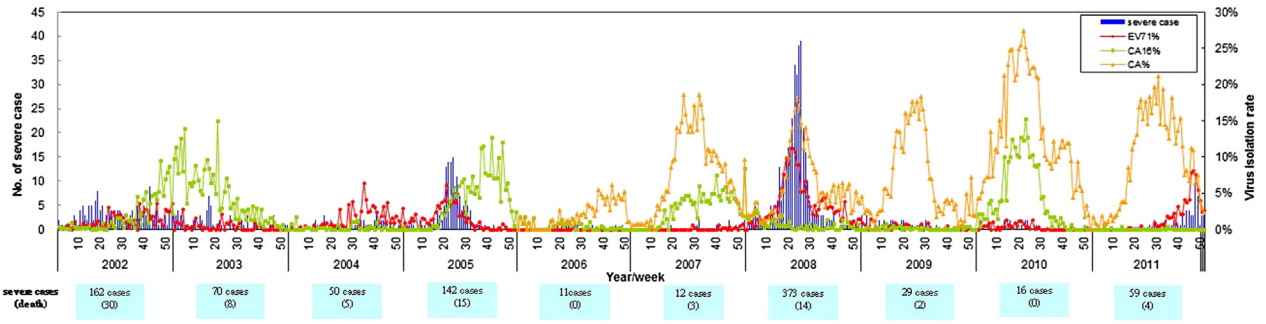

Figure 1 Enterovirus infections with severe complications vs. isolation rate of CA, EV71 and CA16 in Taiwan, 2002-2011.

new detection kits have reduced the number of unidentified viruses significantly.[6]

National Notifiable Surveillance System data show that, although the majority of severe cases were infected by EV71, other enteroviruses also caused severe complications in newborns, including CB3 (in 1999, 2000 and 2005), Echo 4 and Echo 6 (in 2001). The distribution of enterovirus serotypes isolated from severe cases from 1998 to 2011 were EV71 (80.2%), CB3 (3.8%) and CA16 (1.3%). The distribution of lethal cases were EV71 (76.0%), CB3 (3.4%) and Echo 6 (2.9%).

Fig. 1 illustrates trends from 2002 to 2011, based on data from contracted virological laboratories and the national notifiable disease surveillance system. It is clear that CA16 and EV71 were the most prevalent virus types, and the trends of severe case numbers and isolation rate of EV71 are consistent. However, the epidemic cycle for EV71 was irregular, ranging from 2—4 years. CA serogroups such as CA6, CA10, CA4, CA5 and CA9 with low virulence were the main epidemic strains in 2007 and 2009—2011 (data not shown).

EV71 is clearly more virulent than other enteroviruses.[1,7] Research to develop an EV71 vaccine has been actively pursued in Taiwan, China and Singapore. Such vaccines are in clinical trials in these countries and are expected to be marketed within 5 to 10 years.[7,8] However, CA2-8, 10, 12 and 14 can also cause HFMD,[2] and the current vaccines do not address this threat for several reasons. First, the relationship between severe cases and virus types shown in Fig. 1 indicates that 80% of severe cases were caused by EV71. Second, while it is true that including CA16 or other CA serogroups in vaccine components can reduce the incidence of HFMD, the experiments needed on cross-reactions in bivalent or multivalent vaccines, is time-consuming, and will delay the release of vaccines.

EV71 has only one serotype, but it can be further classified into three genogroups and 11 subgenotypes (A, B1—B5 and C1—C5). In Taiwan, various subgenotypes have been isolated: C2/B4/C4 in 1998, B4 in 1999—2003, C4 in 2004—2005, C5 in 2006, C5/B5 in 2007, B5 in 2008—2009, C4 (closely related to the Chinese strain) in 2010 and C4/B5 in 2011. Surveillance data in Taiwan did not show a significant relationship between the subgenotypes and CNS complications.[8] This issue deserves further study, because whether or not the neutralizing antibodies from different subgenotypes of EV71 can provide enough immunity protection, is one of the critical factors for evaluating vaccine candidates.[1]

In conclusion, the development of a monovalent vaccine against EV71 obtains a much higher cost-benefit value than a bivalent or multivalent vaccine, because EV71 is known to be the major cause of severe enteroviral cases.[9] Other enteroviral serotypes, such as CB3, Echo 4 and Echo 6, may also cause neonatal severe complication or deaths, but their epidemic periods are uncertain and the disease burden incurred on the public health system is currently tolerable. Therefore, even though EV71 vaccine will be available soon, systemic enterovirus surveillance and development of diagnostic technology should be continued and improved to monitor evolving serotypes, with the hope of preventing enterovirus epidemics.

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